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PATENT DOCKET NO.: PI862R1C1

REMARKS

At the time of the Office Action dated 4/15/2004, claims 1-23 were pending in the instant application and claims 6-8 were withdrawn from consideration. Applicants herein cancel claims 6-9, 13, 21 and 23 (first occurrence); amend claims 1, 14 and 22-23; and add new claims 24-27. The Examiner noted that there were two claims 23 originally filed, and the first of these is herein cancelled while the second is maintained. Upon entry of the amendments, cancellations, and new claims the instant application will have pending claims 1-5, 12, 14-20, and 22-27. The amendments and new claims are fully supported in the specification and do not introduce new matter.

Allowable Subject Matter

Applicants thank the Examiner for his indication of allowability of claims directed to the elected compounds.

Priority

Applicants have amended the specification herein to comply with 37 CFR 1.78(a)(2) and (a)(5) by inserting below the title a new paragraph making specific reference to the prior applications to which priority is claimed.

Election / Restriction Requirement

The claims are subject to restriction and election of species requirement. Applicants confirm election with traverse of the invention of group I, claims 1-5 and 9-23, drawn to compounds, pharmaceutical compositions and methods pertaining to formula (I) where Cy represents a non-aromatic heterocycle; X represents -CH₂-NR₆-divalent hydrocarbon chain; and L represents a

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divalent hydrocarbon chain. Applicants herein cancel withdrawn claims 6-8 and have amended the pending claims to conform with the restriction requirement.

Rejections under 35 USC §112, 1nd paragraph

Claims 21-23 were rejected under 35 USC 112 1st paragraph, the claims allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Applicants respectfully disagree and assert that the Examiner has failed to meet his burden of presenting a *prima facie* case for lack of enablement.

In order to make a rejection of lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided by the specification for the claimed invention. It is the Examiner's "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." (*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993)). Furthermore, an enablement rejection is improper in the absence of the examiner providing evidence or reasoning to support such a rejection. "it is incumbent upon the Patent Office, whenever a rejection on this basis [§112, first paragraph] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to backup assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." (*In re Marzocchi*, 439 F.2d at 224, 169 USPQ 370).

The Examiner asserts that the application only discloses the results of an *in vitro* activity in example 11 and that "in vitro activity of a compound does not necessarily correlate with their *in vivo* activity since *in vivo* activity is influenced by various factors such as absorption, metabolism etc.". However, the Examiner's assertion is merely speculation without any evidence or reasoning to assert that the particular *in vitro* assay in example 11 is not predictive of

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in vivo activity. It is well established that the interaction between LFA-1 and ICAMs contribute to the initiation and maintenance of multiple processes, including activation of T-lymphocytes, adhesion of T-lymphocytes to endothelial cells, and migration of T-lymphocytes to sites of inflammation. It is also well established that inhibition of this interaction of LFA-1 and ICAM is useful in the treatment of inflammatory disorders. For example, an anti-CD11a monoclonal antibody known as Raptiva® that inhibits the binding of LFA-1 to ICAM-1 has been approved for the treatment of the inflammatory disease psoriasis.

The Examiner goes on to state that there are no working examples of the compounds in animal models and that because the claims encompass many discreet compounds it would require undue experimentation to demonstrate their effectiveness in known animal models where LFA-1 is implicated. However, this is not a proper basis for an enablement rejection, particularly when no evidence has been provided to dispute the predictability of the in vitro assay disclosed in example 11. Indeed, a patent specification need not contain even a single working example (*In re Borkowski*, 422 F.2d 904, 164 USPQ 642, 646 (CCPA 1970).

For the reasons presented herein the Applicants assert that the Examiner has not met the burden of providing a *prima facie* case for lack of enablement and respectfully request withdrawal of the rejection.

Rejections under 35 USC §112, 2nd paragraph

Claims 1-5 and 9-23 stand rejected under 35 USC 112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

The term "heterocycle" in the definition of variables Cy, Y and R1 is alleged to be indefinite without reciting the size of the ring, and the number and types of heteroatoms present. Applicants respectfully disagree. "If the claims when read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more."

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(Miles Laboratories, Inc. v. Shandon, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993)). The skilled artisan would understand the scope of the term "heterocycle" when read in light of the specification. This is evident from the fact the USPTO routinely issues claims incorporating the term without further description. Indeed, the present Examiner issued such claims in US patent 6,667,318 from which the instant application claims priority.

The phrase "hydrocarbon chain" in the definition of variables X and L is alleged to be indefinite without reciting chain length and degree of saturation. Applicants disagree. "Hydrocarbon chain" is a common organic chemistry phrase and is understood by the skilled artisan. Again, it is noted that the present Examiner issued claims incorporating this phrase in US patent 6,667,318 from which the instant application claims priority.

The proviso in claim 1 in which variable X is other than cyclohexyl is a typographical error. It is apparent the proviso applies to variable Cy not X. Nevertheless, the elected compounds do not include carbocycles at variable Cy, therefore Applicants have deleted the proviso thereby rendering the rejection moot.

Claim 21 directed to a method of inhibiting binding of LFA-1 to a protein ligand was rejected as allegedly being indefinite for failing to specify whether the method is *in vitro* or *in vivo*. It is the Applicants' position that the skilled artisan would understand that the claim is not limited to one or the other and is therefore not indefinite. The Examiner found the term "protein ligand" to lacking meaning. The term is routinely used and would be understood in the present context to mean a protein that binds to LFA-1 such as ICAM-1, -2 and -3. However, in the interest of advancing prosecution of the instant application Applicants have cancelled claim 21 without prejudice to its presentation in a continuing application.

Claim 22 was rejected as allegedly being indefinite for failing to specify the diseases or conditions mediated by LFA-1. Applicants disagree, however, in the interest advancing prosecution of the application, Applicants have amended claim 22 to recite particular inflammatory disease states or conditions. Further, Applicants have amended the claim to specify that the disease states or conditions are mediated by LFA-1 binding to an ICAM protein

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ligand. Support for the amendment can be found in the specification, for example, on page 4, lines 27-30.

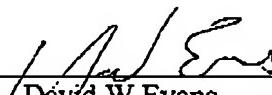
The Examiner noted that there were two claims numbered 23 in the application as filed. Applicants have deleted the first instance of claim 23 and have maintained the second instance which has been amended herein.

In view of Applicants' amendments and remarks presented above, the claims are believed to be in condition for allowance and notice thereof is respectfully requested.

Respectfully submitted,

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*A copy of a document pursuant to 37 C.F.R. § 10.9(b) is attached as proof of the authorization of the above to prosecute the attached application. The original of this document is on file in the Office of Enrollment and Discipline.